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1EN2/113

EXAMINER

SEARCHER

ART UNIT

PAPER NUMBER

1812

DATE MAILED: 12/12/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

This application has been examined Responsive to communication filed on 5/13/96 This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. Notice of References Cited by Examiner, PTO-892.
2. Notice of Draftsman's Patent Drawing Review, PTO-948.
3. Notice of Art Cited by Applicant, PTO-1449.
4. Notice of Informal Patent Application, PTO-152.
5. Information on How to Effect Drawing Changes, PTO-1474.
6.

Part II SUMMARY OF ACTION

1. Claims 12,6,17 are pending in the application.

Of the above, claims _____ are withdrawn from consideration.

2. Claims 3-5, 7-16, 18-37 have been cancelled.

3. Claims _____ are allowed.

4. Claims 12,6,17 are rejected.

5. Claims _____ are objected to.

6. Claims _____ are subject to restriction or election requirement.

7. This application has been filed with Informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. Formal drawings are required in response to this Office action.

9. The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are acceptable; not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been approved by the examiner; disapproved by the examiner (see explanation).

11. The proposed drawing correction, filed _____, has been approved; disapproved (see explanation).

12. Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has been received not been received. been filed in parent application, serial no. _____; filed on _____.

13. Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. Other

423/94.1
12/10/96

EXAMINER'S ACTION

Part III: Detailed Office Action

Claims 1, 2, 6 and 17 are pending and under consideration.

Formal Matters:

5 ✓ The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The disclosure is objected to because of the following informalities. Appropriate correction is required for **each** item:

10 ✓ -The Brief Description of the Figures should refer specifically to each individual figure. Specifically, the description of Figure 12 should read..."Figures 12A-12C show...".

✓ -At page 19 line 32 the word "deletions" is misspelled; at page 32 line 15 "possess" is misspelled; page 32, line 36 "biologically" is misspelled. Additional errors appear at page 35, lines 19, 25 and 32, page 38, line 12 and page 43, line 25 ("a" should read --at--). In addition 15 to the specifically pointed out errors, the entire specification should be thoroughly reviewed for spelling errors.

-The pendency status of all applications to which reference is made at the first page of the specification should be updated.

20 ✓ -At page 11, lines 31-32 the specification states "common β -subunit for the three α -subunits IL-3R α and GM-CSF-R"; it would appear that there are two, not three α subunits which utilize the common β .

✓ -Claim 17 is objected to for using the abbreviated terms "hML" and "EPO". Such terms should appear in their entirety at the first appearance in the claims, e.g. "human mpl ligand (hML)".

Appropriate correction is required for each of the above items.

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37 CFR 1.822(j) provides that nucleotide sequences shall only be represented by a single strand, in the 5' to 3' direction, from left to right. That is, double stranded nucleotides shall not be represented in the "Sequence Listing." A double stranded nucleotide may be represented as

two single stranded nucleotides, and any relationship between the two may be shown in the drawings. It is noted that SEQ ID NO: 5 has reversed polarity; that is, it depicts the complementary strand to SEQ ID NOs:4 in 3' -> 5' orientation, rather than giving the sequences in 5' -> 3' orientation as required by 37 CFR 1.822(j). The sequence listing and CRF should be 5 amended to reflect the proper polarity as required by 37 CFR 1.822(j). Applicants are reminded that, in submitting an amended CRF diskette, *the entire set of sequences* should be resubmitted (i.e. send a complete sequence listing on a single diskette) to avoid confusion. Please see the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Failure to comply with these requirements 10 within the time period set for response to this Office Action will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the 15 response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Double Patenting Rejections:

It is noted that this application is a member of a large family of applications, including 20 serial numbers 08/196689, 08/223263, 08/249376, 08/374540, 08/348657, 08/348658, 08/425016, and 08/498849 as well as the divisional applications derived from each of the aforementioned cases. Myriad provisional statutory and obviousness type double patenting rejections are applicable between the claims of the instant application and its various copending applications. It is beyond the resources of the PTO to establish each and every possible double-patenting 25 rejection which might be made among the pending claims. 37 C.F.R. § 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. See M.P.E.P. § 822. In the instant case, all double patenting rejections, both statutory (35 U.S.C. §101) and obvious-

type, are hereby held in abeyance until such time as this application is allowed. At the time of allowance, applicants will be required to cancel conflicting claims or file appropriate terminal disclaimers, as applicable.

5 **Objections and Rejections under 35 U.S.C. §112:**

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

10 The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15 Enablement is not commensurate in scope with the claims. The disclosure is enabling only for claims limited in scope to full-length, native *mpl* ligands, ligands which are truncated to consist only of the EPO-like domain, the specific truncated forms recited in claim 6, and ligands having a deletion corresponding to amino acids 111-114 of the human *mpl* ligand. See M.P.E.P. §§ 706.03(n) and 706.03(z).

20 Enablement is not commensurate in scope with claims to all possible "substantially homogeneous *mpl* ligand polypeptide(s)" nor compositions comprising such. In one respect, the claims may be interpreted as reading on the disclosed proteins and all fragments thereof that meet the limitation of being polypeptides. While the current specification as filed discloses human, murine and porcine *mpl* ligand, the specification does not teach how to use all possible fragments of those proteins (or even a subset thereof which would be commensurate in scope with the claims), many of which would not have biological activity. In another respect, the phrase "substantially homogeneous *mpl* ligand polypeptide(s)" may be interpreted as reading on any possible ligand to *mpl*. The Examiner notes that "*mpl* ligand" is defined at page 21 of the specification as being a protein that (a) binds *mpl*, and (b) has "a biological property of the *mpl* ligand defined below". Also at pages 22-23 of the specification, "biological property" is defined as including possession of an epitope or antigenic site that cross-reacts with an anti-*mpl* ligand antibody. The teachings of the specification as filed are not commensurate in scope with such

claims with respect to both making or using such proteins, and only enable the specific proteins disclosed therein. While the current specification as filed discloses distinct species of protein which stimulate ^3H thymidine incorporation in Ba/F3-*mpl* cells and/or *in vitro* megakaryocytopoiesis, the specification does not teach how to use all possible fragments of those proteins (or even a subset thereof which would be commensurate in scope with the claims), many of which would not have biological activity, nor does the specification provide guidance as to which fragments would be reasonably expected to retain "a biological function", other than the disclosure that a soluble form of the protein consisting only of the EPO-like domain retains activity. It is noted that the envisioned scope of "fragments" as defined in the specification includes all species which are altered by either the deletion of one or more amino acids, or removal of glycosylation. However, there is insufficient guidance in the specification as to which portions of the protein would be amenable to such deletions, nor whether or not glycosylation is required for activity. The specification does not teach what the epitopic portions of the protein are, and in fact, does not disclose the production of any antibodies that would allow determination of such epitopic regions. Further, such language reads on mimotopes, which share antigenicity but not necessarily any sequence identity or biological activity with the disclosed protein. As the specification does not teach how to make or use a number of species that would be commensurate in scope with the claims, it is found that it would require undue experimentation practice the invention in a manner commensurate in scope with the claims, given the lack of guidance in the specification and the very broad scope of the claims.

The Examiner notes that the description of claimed proteins via a single biological function (in this case that of either binding *mpl* or sharing an epitope with the disclosed ligand, or alternatively being *non-immunogenic*) is similar to the situation in *Ex parte Maizel* (27 USPQ2d 1662 at 1665) in which it was found that:

Appellants have not chosen to claim the DNA by what it is but, rather, by what it does, i.e., encoding either a protein exhibiting certain characteristics, *or* a biologically functional equivalent thereof. Appellants' claims might be analogized to a single means claim of the type disparaged by the Court of Customs and Patent Appeals in *In re Hyatt*, 708F.2d 712, 218 USPQ 195 (Fed. Cir. 1983). The

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problem with the phrase "biologically functional equivalent thereof" is that it covers any conceivable means, i.e., cell or DNA, which achieves the stated biological result while the specification discloses, at most, only a specific DNA segment known to the inventor. Clearly the disclosure is not commensurate in scope with the claims."

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In the current instance, the claims do not positively identify the protein which is the basis for the currently claimed invention, but rather define such in terms of its antigenicity (or lack thereof) or alternatively its biological activity. Therefore, the currently pending claims are analogous to the DNA claims in *Maizel*, in which the DNA was defined by the biological activity of the protein it encoded. In the current case, it is the protein itself which is being defined by biological function.

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Finally, enablement is not commensurate in scope with claims to chimeric peptides of up to 157 hML residues substituted with one or more, but not all, corresponding EPO residues, as shown in Figure 10. It is noted that such language, which appears in claim 17, encompasses a number of species n , represented by the following formula: $n=(157-35)!-1$. Introduction of the possibility of *adding*, rather than just substituting, residues increases this number of species exponentially. It would require undue experimentation to synthesize and test all such species to determine which of the several possible functions, if any, each retained, and further, the current specification as filed does not provide sufficient guidance to allow the ordinary artisan to determine which species would be functional, and how to use such, including the "non-functional" species. Finally, it is noted that numerous of the claimed species would be more "EPO-like" than they would be "*mpl* ligand-like"; the specification does not teach how to use such "EPO-like" proteins, nor does it provide guidance as to where the threshold between "EPO-like" and "*mpl* ligand-like" would be expected to be.

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Claims 1, 2 and 17 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 2, 6 and 17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite because, without reference to any specific species, one could not determine the metes and bounds of what would constitute a "variant" of the polypeptide of claim 5 1.

Claim 6 is indefinite for inclusion of a "fragment" comprising residues 1-332, which would not be a fragment, but a full-length protein.

Claim 17 is indefinite for failing to set forth that which applicant sees as the invention. 10 Specifically, although the claim recites a "chimera" comprising amino acid residues (and therefore at least partially proteinaceous in nature), it is not clear what else the chimera might comprise, for example non-proteinaceous components. Amendment to recite "A chimeric protein" would be remedial.

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Prior Art:

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. (All cited by Applicants, see paper #5)

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McDonald et al. (Exp. Hematol. 17:865-871, 1989) disclose the purification of a protein identified as thrombopoietin from human embryonic kidney cells. The molecular weight of the protein, determined under non-denaturing conditions, is disclosed as being 30,000 kD (see Fig. 10B). At page 870, McDonald et al. teach that TPO is very hydrophilic, is probably a glycoprotein, is stable to β -mercaptoethanol and SDS treatment, and does not deteriorate at pHs of 1 to 8. Although the protein of McDonald shares biological activity with mpl ligand, it appears not to be the same protein, as certain physical characteristics, such as stability to β -mercaptoethanol, differ.

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Methia (Blood 82:1395, 1993) suggests that *mpl* is a cytokine receptor for a thrombopoietic cytokine and suggests using the receptor to clone the ligand. Note the ultimate paragraph (Page 1400) which indicates that it was not known whether *mpl* was a single- or multi-chain receptor.

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Skoda (EMBO 12:2645, 1993) indicates that as of 1993 it was still unknown whether *mpl* had a ligand binding domain, or alternatively required a heterologous protein to form or supply

the ligand binding domain (see paragraph bridging columns of page 2651).

de Sauvage et al. (Nature 369:533), published after the filing date, have correlated the Ba/F3-*mpl* cell proliferation assay used in the current specification with *in vivo* activity.

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Advisory Information:

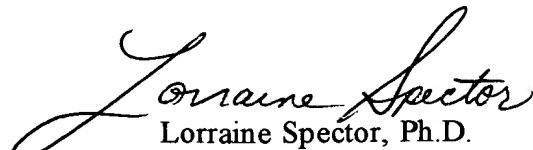
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. 10 Spector can normally be reached Monday through Friday, 8:00 A.M. to 4:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Stephen Walsh, can be reached at (703)308-2957.

15 Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

20 Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The Art Unit 1812 Fax Center number is (703) 308-0294. NOTE: If 25 Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. Please advise the Examiner at the telephone number above when a fax is being transmitted.

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Lorraine Spector, Ph.D.
Patent Examiner

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